UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte CAMPBELL ROGERS, ELAZER R. EDELMAN and DANIEL I. SIMON

Appeal No. 2006-2151
Application No. 08/823,999

HEARD: AUGUST 8, 2006

Before ADAMS, MILLS, and GREEN, Administrative Patent Judges.

GREEN, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134 from the examiner's final rejection of claims 1-6, 8 and 10-12.[1] Claims 1 and 6 are the independent claims on appeal, and read as follows:

[1] Claims 1-12 are pending, with claims 7 and 9 being withdrawn from consideration as being directed to a non-elected invention. Examiner's Answer, page 2. In addition, claims 1-6, 8 and 10-12 "are under consideration as the claims read on ant[i]-Mac-1 (anti-CD11b/CD18) antibodies as the claimed [ ]compound." Id. The full scope of the claimed subject matter, however, is subject to the rejections under 35 U.S.C. § 112, first paragraph, written description and enablement was "for clarity and in the interest of compact prosecution." Id. This application has had a long and tortuous prosecution history, so in the interest of forwarding the prosecution, we will address the merits of both the written description rejection and the enablement rejection as they pertain to the full scope of the claimed subject matter.

1. A method of inhibiting stenosis or reducing stenosis arising from coronary artery bypass surgery, peripheral bypass surgery, or transplantation of cells, tissue or organs or restenosis of a blood vessel following injury to vascular tissue in a region of the blood vessel of a patient in need of treatment thereof, comprising:

administering systemically or at the site of the injury a pharmaceutically acceptable composition comprising a compound which specifically inhibits or reduces leukocyte integrin-mediated adhesion or function,

wherein the integrin is selected from the group consisting of Mac-1 (CDIIb/CD18), LFA-1 (CD11a/CD18), p150,95 (CD11c/CD18), and CD11d/CD18,

wherein the compound is selected from the group consisting of antibodies and antibody fragments that are immunoreactive with the integrins or integrin-ligands and which block the interaction of the integrins or integrin-ligands with vascular cells; molecules which inhibit expression of the integrins or integrin-ligands, and peptides and peptidomimetics derived from the integrins or integrin-ligands which block the interactions of the integrins or integrin-ligands with vascular cells or tissues,

in an amount effective to inhibit or reduce stenosis arising from coronary artery bypass surgery, peripheral bypass surgery, or transplantation of cells, tissues or organs or restenosis of a blood vessel flowing injury to vascular tissue.

6. A method of inhibiting or reducing stenosis arising from, coronary artery bypass surgery, peripheral bypass surgery, or transplantation of cells, tissue or organs or restenosis of a blood vessel following injury to vascular tissue in a region of the blood vessel of a patient in need of treatment thereof, comprising:

administering systemically or at the site of the injury a pharmaceutically acceptable composition comprising a compound which specifically inhibits or reduces leukocyte integrin-mediated adhesion or function,

wherein the integrin is Mac-1 (CD11b/CD18),

wherein the compound is selected from the group consisting of antibodies and antibody fragments that are immunoreactive with the integrins or integrin-ligands and which block the interaction of the integrins or integrin-ligands with vascular cells; molecules which inhibit expression of the integrins or integrin-ligands; and peptides and peptidomimetics derived from the integrins or integrin-ligands which block the interaction of the integrins or integrin-ligands with vascular cells or tissues,

in an amount effective to inhibit or reduce stenosis arising from coronary artery bypass surgery, peripheral bypass surgery, or

transplantation of cells, tissue or organs or restenosis of a blood vessel following injury to vascular tissue.

The following are the grounds of rejection:

I. Claims 1-6, 8, 11 and 12 stand rejected under 35 U.S.C. § 112, first paragraph, on the grounds that the specification does not provide an adequate written description of the claimed invention.

II. Claims 1-6, 8, 11 and 12 stand rejected under 35 U.S.C. § 112. first paragraph, for lack of enablement.

III. Claims 1-6, 8 and 10-12 stand rejected under 35 U.S.C. § 102(a)/(b) as being anticipated by Genetta.[2]

IV. Claims 1-6, 8 and 10 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Simon 1995.[3]

V. Claims 1-6, 8 and 10-12 stand rejected under 35 U.S.C> § 102(e) as being anticipated by Coller.[4]

VI. Claims 1-6, 8, 10-12 stand rejected under 35 U.S.C. § 102(e) as being anticipated by Co.[5]

VII. Claims 1-6, 8 and 10-12 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Todd.[6]

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[2] Genetta et al. (Genetta), "ABCIXIMAB: A New Antiaggregant Used in Angioplasty," The Annals of Pharmacotherapy, Vol. 30, pp. 251-257 (March 1996).

[3] Simon et al. (Simon 1995), "Monoclonal Antibody Directed Against the Platelet IIb/IIIa Receptor Cross-Reacts with the Leukocyte Integrin Mac-1 and Blocks Adhesion to Fibrinogen and ICAM-1," Circulation, Volume 92, Supplement I, Abstract 0519 (1995).

[4] Coller et al. (Coller), U.S. Patent No. 5,976,532, issued November 2, 1999.

[5] Co, U.S. Patent No. 6,210,671 B1, issued April 3, 2001.

[6] Todd, III et al. (Todd), U.S. Patent No. 4,935,234, issued June 19, 1990.

VIII. Claims 1-6, 8 and 10-12 stand rejected under 35 U.S.C. § 103(a) as being obvious over the combination of Co and/or Todd, Simon 1995, Mazzone,[7] Ikeda,[8] Inoue[9] and Rogers.[10]

After review of the record and careful consideration of the issues before us, we reverse the rejection of VI, but affirm I, II, III, VII and VIII. We do not reach the merits of rejections IV and V as those rejections are cumulative to the rejection of III.

BACKGROUND

According to the specification, "[a]ngioplasty, surgery and other vascular interventions are complicated by an accelerated arteriopathy characterized by a rapid growth of cells into the lumen within a short period of time. This growth is often severe enough to jeopardize the blood flow to distal organs." Specification, page 1.

> Injury of arteries in animals induces a process of vascular repair which eventually causes the artery to become narrowed. A thick new layer, or neointima, of smooth muscle cells and inflammatory cells grows within the blood vessel, encroaching on the lumen. This process in animals represents the process which occurs clinically after angioplasty, endovascular stent implantation, organ transplantation, or bypass surgery, which greatly limits the long term successes of these techniques for treating obstructive arterial disease. Animal models of arterial injury and neointimal

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[7] Mazzone et al. (Mazzone), "Increased Expression of Neutrophil and Monocyte Adhesion Molecules in Unstable Coronary Artery Disease," Circulation, Vol. 88, pp. 358-63 (1993).
[8] Ikeda et al. (Ikeda), "Neutrophil activation after percutaneous transluminal coronary angioplasty," American Heart Journal, Vol. 128, pp. 1091-98 (1994).
[9] Inoue et al. (Inoue), "Expression of Polymorphonuclear Leukocyte Adhesion Molecules and Its Clinical Significance in Patients Treated with Percutaneous Transluminal Coronary Angioplasty," J. Am. Coll. Cardiol., Vol. 28, pp. 1127-33 (1996).
[10] Rogers et al. (Rogers), "Inhibition of Experimental Neointimal Hyperplasia and Thrombosis Depends on the Type of Vascular Injury and the Site of Drug Administration," Circulation, Vol. 88, pp. 1215-21 (1993).

> hyperplasia have been used to study the cellular events that lead to restenosis in humans, to devise treatment strategies to suppress tissue growth in an attempt to reduce restenosis and enhance long term clinical results.
>
> Attempts to limit stenosis or restenosis of blood vessels following revascularization have included administration of pharmacologic agents and technical approaches. No pharmacologic agent has yet been shown to reduce restenosis in humans.

Id. at 2.

Thus, the specification notes that "there is a need for compositions and methods of promoting healing of vascular tissue and controlling vascular muscle cell proliferation (hyperplasia) to prevent restenosis of blood vessels after angioplasty, vascular bypass, organ transplantation, or vascular disease, with minimal risk of rapid reocclusion." Id. at 3.

The invention is therefore directed to "[c]ompositions and methods for reducing stenosis or restenosis after revascularization of diseased coronary, peripheral, and cerebral arteries and stenosis or restenosis of surgically-placed bypass grafts or transplanted tissues are described which involve administration of a composition specifically inhibiting integrin-mediated leukocyte adhesion or function, prior to, at the time of and/or subsequent to vascular intervention." Id. at 4.

The specification teaches that leukocyte adhesion or function may be inhibited or reduced by blocking cell surface integrins, more preferably the leukocyte integrins such as Mac-1 or LFA-1. See id.

> Exemplary compounds for inhibiting or reducing leukocyte adhesion or function include antibodies and antibody fragments that are immunoreactive with these integrins or their ligands and

> which inhibit or reduce the binding of integrins or their ligands to vascular cells; molecules which inhibit or reduce the expression of the integrins or their ligands, including nucleic acid regulators such as antisense oligonucleotides, ribozymes and external guide sequences for RNAase P, molecules involved in triplex formation, aptamers, peptides and peptidomimetics derived from the integrins or their ligands which block the interaction of the integrins or their ligands with vascular cells such as peptides and peptidomimetics that block the leukocyte integrin Mac-1. The compounds can be administered systemically or administered directly to the site of vascular injury, most preferably prior to and after injury.

Id. at 4-5.

The specification teaches that "[m]olecules with a given function, catalytic or ligand-binding, can be selected for from a complex mixture of random molecules in what has been referred to as 'in vitro genetics.'" Id. at 14. The specification also teaches that computer assisted drug design may be used to identify compounds useful in the invention. See id. at 15-16. Example 1 of the specification "demonstrates that an antibody to Mac-1 (M 1/70) binds to rabbit peripheral blood mononuclear cells and thereby inhibits ligand binding to Mac-1." Id. at 5. Example 2 "demonstrates the neointimal hyperplasia after both superficial and deep injury was significantly reduced with M1/70 treatment, as compared to both saline and IgG controls." Id.

According to the specification, "[t]hose of skill in the art can readily determine an effective concentration for treating a patient in need thereof typically based on extrapolation from animal data and from correlations established during clinical trials." Id. at 21

> In general, this will result in a patient being treated systemically with the inhibitor of integrin mediated leukocyte adherence or function for between zero and 24 to 48 hours prior to

> surgery or vascular intervention, preferably about two hours, and for a period of time following surgery, typically until healing has occurred, which may be as long as six months following vascular intervention, although more typically will be for four to six weeks or until acute inflammation has subsided.

Id. at 21-22.

PROCEDURAL HISTORY

This is the second time that this appeal has been before the Board.[11] In the Decision mailed April 23, 2003, the panel vacated the pending rejections and remanded the case to the examiner for consideration several issues. Those issues are discussed below, as well how those issued appear to have been resolved.

I. It was recommended that appellants and the examiner clarify what is covered by the terms "stenosis," restenosis," and "dependent restenosis." April 2003 Decision at 3.

The decision cited Taber's[12] for the definition of "stenosis" as "[t]he constriction or narrowing of a passage or orifice," "aortic stenosis" as "[n]arrowing of the aorta or its orifice due to the lesion of the wall with scar formation," and "restenosis" as "[t]he recurrence of a stenotic condition as in a heart valve or vessel." April 2003 Decision at 3; see also Appeal Brief,[13] page 11, Examiner's Answer, page 33.

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[11] The previous panel was Winters, Grimes and Green.
[12] Taber's Cyclopedic Medical Dictionary (Taber's), 18th ed., pp. 130, 1666, and 1825 (1997).
[13] All references to the Appeal Brief are to the Substitute Appeal Brief, dated August 10, 2004.

In response, appellants define "stenosis" as "[n]arrowing of a blood vessel for the first time," "restenosis" as "[r]e-narrowing of a vessel after mechanical intervention for example with balloon, stent, atherectomy or laser," and have removed "dependent restenosis" from the claims. Appeal Brief, pages 10-11.

The examiner also acknowledges the panel's citation to Taber's, and also excerpts Fattori[14] as background. See Examiner's Answer, pages 33-34.

As Taber's has been acknowledged by both appellant and the examiner, and as it sets forth the broadest definition, and as appellants do not point to where in the specification their narrower definition finds support, we will construe "stenosis" and "restenosis" consistent with the definition set forth in Taber's, and as referenced in the April 2003 Decision.

II. The examiner's attention was directed to the Genetta reference. The previous panel noted that Genetta was not part of a prior art rejection, stating that "[t]his is inexplicable because Genetta appears to constitute more relevant prior art than the references which, to date, have been applied against applicants' claims." April 2003 Decision at 4.

In response, the examiner has instituted a prior art rejection over Genetta, as set forth below.

III. The panel noted that appellants had submitted a number of abstracts to rebut the examiner's finding and conclusions, but that it appeared that the examiner was relying on the full text articles, but had not made the full text

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[14] Fattori et al. (Fattori), "Drug-eluting stents in vascular intervention," Lancet, Vol. 361, pp. 247-49 (2003).

articles of record. Thus, it did not appear that the examiner and appellants were on the same page. Thus, the panel recommended that if appellants were to rely on a reference, that the full text article be supplied and be made of record. April 2003 Decision at 4-6.

In response, appellants submitted a "Reply to Order Returning Undocketed Appeal to Examiner" on December 1, 2005, to which was attached the full text of twenty-one separate references.

IV. The panel commented on the examiner's usage of the expression "AND/OR" in his obviousness rejection, noting that "it is unclear just how the references are combined; or how many permutations and combinations of references are relied upon." April 2003 Decision at 6.

At this point in the prosecution, the examiner is maintaining a single obviousness rejection over the combination of Co and/or Todd, Simon 1995, Mazzone, Ikeda, Inoue, and Rogers. That rejection only encompasses three combinations, Simon 1995, Mazzone, Ikeda, Inoue, and Rogers together with Co alone, Todd alone, or the combination of Co and Todd. In the interest of furthering the prosecution, we will address the merits of the rejection. We again caution the examiner, however, to limit the use of the expression "AND/OR" in his obviousness rejections.

V. Finally, the panel noted that "in rejecting the claims for lack of [ ] novelty, the examiner states that 'no more of the reference is required than that it sets forth the substance of the invention' (Paper No. 29, page 7, first and third paragraphs)." April 2003 Decision, page 7. In remanding the application, the

panel requested that "if the examiner adheres to the position that applicants' claims are anticipated within the meaning of 35 U.S.C. § 102, we recommend that the examiner explain how each and every claim limitation is found either expressly or inherently in a single prior art reference." Id.

We again caution the examiner in his use of the phrase "Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention." See, e.g., Examiner's Answer, page 25. In order to further advance the prosecution of this application, we interpret this phrase as recognition that in order to anticipate the claimed invention, the prior art must disclose every limitation of the claimed invention, either explicitly or inherently. The rejections under 35 U.S.C. § 102 set forth in the Examiner's Answer will be analyzed on their merits to determine if they meet that standard.

CLAIM CONSTRUCTION

Claim 1 is drawn to:

> A method of inhibiting stenosis or reducing stenosis arising from coronary artery bypass surgery, peripheral bypass surgery, or transplantation of cells, tissue or organs or restenosis of a blood vessel following injury to vascular tissue in a region of the blood vessel of a patient in need of treatment thereof, comprising:
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> administering systemically or at the site of the injury a pharmaceutically acceptable composition comprising a compound which specifically inhibits or reduces leukocyte integrin-mediated adhesion or function,
>
> wherein the integrin is selected from the group consisting of Mac-1 (CDIIb/CD18), LFA-1 (CD11a/CD18), p150,95 (CD11c/CD18), and CD11d/CD18,
>
> wherein the compound is selected from the group consisting of antibodies and antibody fragments that are immunoreactive with the integrins or integrin-ligands and which block the interaction of the integrins or integrin-ligands with vascular cells; molecules which inhibit expression of the integrins or integrin-ligands, and peptides

> and peptidomimetics derived from the integrins or integrin-ligands which block the interactions of the integrins or integrin-ligands with vascular cells or tissues,
>
> in an amount effective to inhibit or reduce stenosis arising from coronary artery bypass surgery, peripheral bypass surgery, or transplantation of cells, tissues or organs or restenosis of a blood vessel following injury to vascular tissue.

Thus, claim 1 is drawn to a method of administering a compound which "specifically inhibits" or "reduces" leukocyte integrin-mediated adhesion or function, wherein the elected integrin is Mac-1, wherein the compound is selected from the group consisting of "antibodies and antibody fragments that are immunoreactive with the integrins or integrin-ligands and which block the interaction of the integrins or integrin-ligands with vascular cells; molecules which inhibit expression of the integrins or integrin-ligands, and peptides and peptidomimetics derived from the integrins or integrin-ligands which block the interactions of the integrins or integrin-ligands with vascular cells or tissues," and wherein stenosis or restenosis is inhibited or reduced.

Giving the claims the broadest reasonable interpretation, see In re Zletz, 893 F.2d 319, 321, 13 USPQ2d 1320, 1322 (Fed. Cir. 1989) (during ex parte prosecution, claims are to be given their broadest reasonable interpretation consistent with the description of the invention in the specification), the claims read on a compound that "reduces" leukocyte-mediated adhesion or function, wherein there is a resultant inhibition or reduction of stenosis or reduction in restenosis. The claims do not specify any level of inhibition or reduction, thus the claims read on any measurable inhibition or reduction of stenosis or

reduction of restenosis. In addition, the compound must reduce leukocyte integrin-mediated adhesion or function, and must also be a compound such as an antibody and antibody fragment that is immunoreactive with the integrin or integrin-ligand and which block the interaction of the integrin or integrin-ligand with vascular cells. But there is no requirement that the compound reduces leukocyte integrin-mediated adhesion or function through its immunoreactivity with the integrin or integrin ligand. Moreover, "immunoreactive," as defined by Merriam-Webster's on-line Medical Dictionary, is "reacting to particular antigens or haptens."[15] Thus, all that is required is that the compound binds to the integrin or integrin-ligand with any measurable level of specificity.

Note that stenosis and restenosis are construed as set forth in item I of the discussion of the procedural history.

DISCUSSION

WRITTEN DESCRIPTION

Claims 1-6, 8, 11 and 12 stand rejected under 35 U.S.C. § 112, first paragraph, on the grounds that the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the art that the inventor(s) had possession of the claimed invention at the time the application was filed. Examiner's Answer, page 6.

As appellants do not argue the claims separately, we will focus our analysis on independent claim 1. See 37 CFR § 41.37(c)(1)(vii) (2006) (merely

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[15] http://www2.merriam-webster.com/cgi-bin/mwmednlm?book=Medical&va=immunoreactive, website visited December 27, 2006. A copy of the webpage is attached to this opinion.

pointing out differences in what the claims cover is not an argument as to why the claims are separately patentable).

According to the examiner,

> There is insufficient written description encompassing any "compound which specifically inhibits or reduces leukocyte integrin-mediated adhesion or function[", sic] as well as "wherein the integrin is Mac-1 (CD11b/CD18) (see claim 6) in an amount effective to inhibit or reduce stenosis arising from coronary artery bypass surgery, peripheral bypass surgery, or transplantation of cells, tissue or organs or restenosis of a blood vessel[ ] following injury to vascular tissue" currently recited in the instant claims because the relevant identifying characteristics such as structure [or] other physical and/or chemical characteristics of the claimed "compounds" including "antibodies, molecules, peptides and peptidomimemtics"[ ] as currently claimed, or "ligands, proteins, antisense oligonucleotides and ribozymes"[ ] as currently disclosed, encompass . . . distinct adhesion molecules (and pathways) and inhibitory compounds, wherein the compounds as well as the adhesion molecules differ in structure and modes of action (see Composition on pages 9-20 of the instant specification). The "compounds" encompass distinct and diverse structures and do not encompass common structural elements essential to the common utility of [ ]specifically inhibiting or reducing leukocyte integrin-mediated adhesion or function in an amount effective to inhibit or reduce stenosis or restenosis in patients undergoing the cardiovascular surgeries and procedures encompassed by the claimed methods.

Examiner's Answer, pages 6-7 (emphasis in original).

The examiner further notes that "[t]he reliance on the disclosed limited number of known adhesion molecules or adhesion molecule-specific antibodies does not support the written description of any 'compound which specifically inhibits or reduces leukocyte integrin-mediated adhesion or function', including any 'antibody, molecule, peptide or peptidomimetic'." Id. at 7 (emphasis in original). According to the examiner, the specification appears to disclose only a

single peptide, which is a fibrinogen fragment that modifies fibrinogen binding to Mac-1, described by Altieri, [16] as well as only a single antibody, the M1/70 antibody which binds to Mac-1, described in Examples 1 and 2 of the specification. See id. at 11.

As set forth by the examiner, appellants appear to be relying on the following for written description support: (a) random generation of integrin or integrin encoding sequence binding molecules (citing pages 14-15 of the specification); (b) computer modeling technology (citing page 15 of the specification); and (c) theoretical calculations and empirical findings for providing guidance for the design of oligonucleotides that inhibit gene expression (citing page 18 of the specification). Examiner's Answer, page 11. Appellants, according to the examiner, also rely on their disclosure of assays for testing compounds that may be useful in the claimed therapeutic method. See id. There is no written description, the examiner contends, of such inhibitory peptides (other than the one disclosed by Altieri), peptidomimetics, molecules or oligonucleotides that are useful in the claimed therapeutic methods. See id.

The examiner concludes:

> There is insufficient written description of the claimed "compounds" broadly encompassed by the claimed invention. There is lack of disclosure of sufficient relevant identifying characteristics coupled with a known or disclosed correlation between function and structure of the broadly diverse compounds employed in the claimed methods.

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[16] Altieri et al. (Altieri), "The Structural Motif Glycine 190-Valine 202 of the Fibrinogen γ Chain Interacts with CD11b/CD18 Integrin ($\alpha_M\beta_2$, Mac-1) and Promotes Leukocyte Adhesion," The Journal of Biological Chemistry, Vol. 268, pp. 1847-1853 (1993).

> While the specification discloses a starting point for screening or testing for compounds that inhibit or reduce leukocyte integrin-ligand interactions, the instant disclosure does not set forth sufficient procedures that will necessarily lead to discovery for such a compound and it does not identify suitable members of compounds such as peptidomimetics, antisense oligonucleotides, nucleic acid regulators, molecules from a complex mixture of random molecules, natural products and synthetic chemical compounds to provide a sufficient number of species to support the claimed genus of "compounds".
>
> The application does no more that describe the desired function of the claimed compounds broadly encompassed by the claimed invention and does not contain sufficient information by which a person of ordinary skill in the art would understand that the inventors possessed the claimed invention.

Id. at 12 (emphasis removed).

In Enzo Biochem, Inc. v. Gen-Probe Inc., 323 F.3d 956, 63 USPQ2d 1609 (Fed. Cir. 2002), the Federal Circuit adopted a portion of the Guidelines proffered by the United States Patent and Trademark Office (USPTO). The court stated that:

> The written description requirement can be met by "showing that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics . . . i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of characteristics."

Enzo Biochem, 323 F.3d at 964, 63 USPQ2d at 1613 (citing Guidelines for Examination of Patent Applications Under the 35 U.S.C. § 112, ¶ 1 "Written Description Requirement, 66 Fed. Reg. 1099, 1106 (January 5, 2001)).

In University of Rochester v. G.D. Searle & Co., Inc., 358 F.3d 916, 69 USPQ2d 1886, (Fed. Cir. 2004) the Court of Appeals for the Federal Circuit held that claims drawn to methods of inhibiting PGHS-2 activity by administering a

non-steroidal compound that inhibits activity of prostaglandin H synthase-2 were invalid for failing to comply with the written description requirement of 35 U.S.C. § 112, first paragraph. See 358 F.2d at 917-18, 69 USPQ2d at 1887-88.

The University of Rochester court made clear that cases such as Enzo do not apply only to claims to genetic material, making clear that the written description requirement applies to all types of inventions. See 358 F.2d at 925, 69 USPQ2d at 1893-94. Moreover, while disclosure of a DNA sequence may support claims to complementary molecules that can hybridize to it due to the complementarity of genetic material, "[t]he same is not necessarily true of the chemical arts more generally." See id. Thus, "[a] description of what a material does, rather that of what it is, normally does not suffice." See 358 F.2d at 923, 69 USPQ2d at 1892 (citation omitted).

Claim 1 is drawn to (emphasis added):

> A method of inhibiting stenosis or reducing stenosis arising from coronary artery bypass surgery, peripheral bypass surgery, or transplantation of cells, tissue or organs or restenosis of a blood vessel following injury to vascular tissue in a region of the blood vessel of a patient in need of treatment thereof, comprising:
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> administering systemically or at the site of the injury a pharmaceutically acceptable composition comprising a compound which specifically inhibits or reduces leukocyte integrin-mediated adhesion or function,
>
> wherein the integrin is selected from the group consisting of Mac-1 (CDIIb/CD18), LFA-1 (CD11a/CD18), p150,95 (CD11c/CD18), and CD11d/CD18,
>
> wherein the compound is selected from the group consisting of antibodies and antibody fragments that are immunoreactive with the integrins or integrin-ligands and which block the interaction of the integrins or integrin-ligands with vascular cells; molecules which inhibit expression of the integrins or integrin-ligands, and peptides and peptidomimetics derived from the integrins or integrin-ligands

> which block the interactions of the integrins or integrin-ligands with vascular cells or tissues,
>
> in an amount effective to inhibit or reduce stenosis arising from coronary artery bypass surgery, peripheral bypass surgery, or transplantation of cells, tissues or organs or restenosis of a blood vessel following injury to vascular tissue.

Thus, as noted by the examiner, the claim encompasses a broad range of compounds, wherein the compounds are described only by function, i.e., wherein the compound "specifically inhibits or reduces leukocyte integrin-mediated adhesion or function", and "wherein the compound is selected from the group consisting of antibodies and antibody fragments that are immunoreactive with the integrins or integrin-ligands and which block the interaction of the integrins or integrin-ligands with vascular cells; molecules which inhibit expression of the integrins or integrin-ligands, and peptides and peptidomimetics derived from the integrins or integrin-ligands which block the interactions of the integrins or integrin-ligands with vascular cells or tissues."

As also noted by the specification, only two specific compounds that fall within that broad genus are described: the peptide of Altieri and anti-Mac M 1/70 antibody, two very structurally different compounds. The disclosure, however, does not set forth any structural relationship between the classes of the compounds that may be used as the therapeutic compound and the claimed therapeutic result, i.e., reduction of stenosis and restenosis. As noted by the examiner, the broad classes of compounds useful in the claimed therapeutic method are only described by function. Thus, we find that the specification does not contain a written description of the claimed invention, in that the disclosure

does not reasonably convey to one skilled in the art that the inventor(s) had possession of the claimed invention at the time the application was filed, and the rejection is affirmed.

> Appellants argue that:
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> Detailed description is provided for compounds such as antibodies or antibody fragments (p 9-11), peptide and peptidomimetic compounds (p11-p13) and nucleic acid regulators (p16-19) that inhibit or reduce leukocyte integrin-mediated adhesion or function. These compounds share the common feature that they all bind integrins or their ligands. These compounds were known and available as of the date of filing – it was not the discovery of these compounds, but of their selection and utility that appellants claim. One of skill in the art would know of other such compounds and how to make them without undue experimentation.

Appeal Brief, page 22.

> Moreover, according to appellants, the specification also describes computer aided drug design on page 15, wherein one can model drugs and their interactions with the integrins. Appellants contend that the "method describes a concrete means by which one can model drugs and their interactions with the integrins. This method describes a concrete means by which one can obtain a wide range of compounds that reduce or inhibit leukocyte integrin-mediated adhesion or function." Id.

Finally, appellants assert that the specification describes several species, and that adequate description of claims to species support the claims to the genus, and thus the legal requirements for adequate written description are met. See id.

Appellants' arguments are not found to be convincing. In the University of Rochester decision, the court noted that the disclosure of a DNA sequence might support a claim to complementary molecules that can hybridize to it. See Rochester, 358 F.2d at 925, 69 USPQ2d at 1894. As to the chemical arts, however, the court stated that the same is not necessarily true, and that even with a three-dimensional structure, one skilled in the art may not be able to predict what compounds may bind to that structure and inhibit its interactions, especially in the 1993-1995 time period that led to the filing of the patent at issue in that case. See id.

As in the University of Rochester decision of the Federal Circuit, the compounds required by the instantly claimed therapeutic methods are described by the specification only by function, not by structure. The description of antibodies or antibody fragments, peptide and peptidomimetic compounds and nucleic acid regulators that inhibit or reduce leukocyte integrin-mediated adhesion or function is very general, with the only two specific species described being the M1/70 antibody and the peptide disclosed in Altieri. Appellant's genus of compounds encompassed by claim 1 is very broad and structurally diverse, encompassing proteins such as antibodies, peptides, peptidomimetics, small molecules, and regulators of gene expression such as anti-sense oligonucleotides and ribozymes, and that limited description of specific species, which have no structural relationship to one another, is not deemed to support the claimed genus. Moreover, although appellants assert that the specification also describes computer aided drug design, wherein one can model drugs and

their interactions with the integrins, the filing date of the instant application is 1997, not long after the 1993-1995 period discussed by the court in University of Rochester, and, as in that case, appellants do not offer any evidence that it was well within the level of skill in the art to determine compounds using such computer modeling methods that would be effective in the claimed therapeutic methods.

As to claim 8 and 10, appellants argue that claim 8 limits the compounds to antibody and antibody fragments, and is thus not "any compound." See Reply Brief,[17] page 9. Claim 10, according to appellants, is limited to antibodies specifically reactive with Mac-1, and reduced to practice in Example 2 of the specification, thus clearly meeting the requirements for adequate written description. See id.

These arguments have not been considered, as appellants, although asserting in the Appeal Brief that the claims did not stand or fall together, see Appeal Brief, pages 6-7, did not argue claims 8 and 10 independently in the Appeal Brief, but have first presented arguments as to the separate patentability of those claims in the Reply Brief. See 37 CFR 41.37 (c)(1)(vii) (2006).

ENABLEMENT

Claims 1-6, 8, 11, and 12 stand rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter that was not described in the

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[17] All references to the "Reply Brief" are to the "Reply Brief to Examiner's Answer," dated February 9, 2005.

specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

With respect to the enablement rejection, as appellants have not argued the claims separately in the Appeal Brief, they stand or fall together. See In re Dance, 160 F.3d 1339, 1340 n.2, 48 USPQ2d 1635, 1636 n.2 (Fed. Cir. 1998) (noting that dependent claims not argued separately on the merits rise or fall with the independent claim to which they relate). Therefore, we focus our analysis on independent claim 1.

According to the examiner:

> The claimed "compounds" encompass any compound, integrin, ligand, molecule, peptide, or peptidomimetic or others disclosed on pages 9-20 of the instant specification, which are disclosed and asserted to be capable of inhibiting or reducing leukocyte-integrin-mediated adhesion to inhibit or reduce stenosis or restenosis. However, the claims do not recite sufficient structural elements or specificity for the compounds" encompassed by the claimed methods. The specification does not provide sufficient guidance and direction to identify and enable any "compound" which might inhibit or reduce leukocyte-integrin-mediated adhesion which inhibits or reduces stenosis or restenosis, including achieving these therapeutic endpoints in human patients in need thereof.

Examiner's Answer, page 14 (emphasis in original). The examiner elaborates further that the claims encompass targeting a variety on integrin members using "a variety of structural[ly] diverse compounds (e.g. antibodies, molecules, peptides, peptidomimetics, nucleic acid regulators, antisense oligonucleotides, ribozymes)." Id. at 18 (emphasis removed).

After commenting that "[p]harmaceutical therapies in the absence of in vivo clinical data are unpredictable," id. at 14, the examiner cites several

references supporting his conclusion that the specification fails to enable one skilled in the art to practice the claimed invention, see id. at 15-17. For example, Pimanda[18] is cited for teaching that in addressing the problem of restenosis, drugs that have been tested in animal models, particularly pigs, have not shown benefits in humans. See id. at 15. Welt[19] is also cited for teaching that drugs that show promise in animal models often are not effective in humans. See id. at 16 Fattori is cited for teaching that "'many different biological mechanisms contribute to restenosis and drugs that target only one pathway for a restricted period may have little value in multifactorial process.'" Id. at 15 (emphasis provided by examiner) (quoting Fattori at 247). The examiner also cites Topol,[20] a reference provided by appellants, for teaching "that a large number of pharmacological agents have failed to reduce restenosis or improve long-term outcomes and the only large-scale trial that reported an effect was the 23% reduction in clinical recurrence at 6 months using abcixmab, a monoclonal fragment against the β3 integrin." Id. at 16 (emphasis in original).

As to the teachings provided by the specification, the examiner notes that the specification

> relies upon screening for peptide and peptidomimetic compounds . . . as well as screening for antisense oligonucleotides, nucleic acid regulators, molecules from a complex mixture of random molecules, natural products and synthetic chemical compounds

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[18] Pimanda et al. (Pimanda), "Novel and Emerging Therapies in Cardiology and Haematology," Current Drug Targets-Cardiovascular & Haematological Disorders, Vol. 3, pp. 101-23 (2003).

[19] Welt et al. (Welt), "Inflammation and Restenosis in the Stent Era," Arterioscler. Thromb. Vasc. Biol. Vol. 22, pp. 1769-74 (2002).

[20] Topol et al. (Topol), "Long-term Protection From Myocardial Ischemic Events in a Randomized Trial of Brief Integrin β_3 Blockade With Percutaneous Coronary Intervention," JAMA, Vol. 278, pp. 479-84 (1997).

> . . . . The specification appears to disclose only one peptide, that is, a particular fibrinogen fragment which modifies fibrinogen to Mac-1 described by [Altieri] . . . . As indicated above, the only observation provided by the specification as filed is the administration of the anti-Mac-1 antibody M1/70 in an experimental animal model.

Id. at 17-18.

The examiner assets that the record lacks evidence that data from a single compound such as the M1/70 antibody can be extrapolated to the diverse range of integrins and compounds being claimed to inhibit or reduce stenosis or restenosis. See id. at 18. In support, the examiner cites the use of heparin, which can bind to Mac-1, but does not result in the inhibition of stenosis or restenosis in humans, despite success in animal model systems. See id., see also page 17 (citing Diamond[21] and Dangas[22] for their teaching that heparin binds Mac-1, but does not show beneficial effects on restenosis). Moreover, as to the screening, the examiner acknowledges that the specification teaches "assays for determining whether a given compound has certain desired characteristics and identifies some broad categories of compounds that might work," but contends that the "description of screening assays without more precise guidelines amount to little more that a starting point, a direction for further research." Id. at 19 (emphasis removed).

The examiner concludes:

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[21] Diamond et al. (Diamond), "Heparin is an Adhesive Ligand for the Leukocyte Integrin Mac-1 (CD11b/CD18)," The Journal of Cell Biology, Vol. 130, pp. 1473-1482 (1995).
[22] Dangas et al. (Dangas), "Management of restenosis after coronary intervention," Am. Heart J., Vol. 132, pp. 428-36 (1996).

> In view of the lack of predictability of the art to which the invention pertains the lack of established clinical protocols for effective therapies for inhibiting restenosis and stenosis, undue experimentation would be required to practice the claimed methods with a reasonable expectation of success, absent a specific and detailed description in applicant's of how to effectively practice the claimed methods and absent working examples providing evidence which is reasonably predictive for the breadth of "compounds" which specifically inhibits or reduces leukocyte-integrin-mediated adhesion that reduce or inhibit stenosis or restenosis in patients undergoing certain cardiovascular surgeries and procedures.

Id. at 19-20.

"When rejecting a claim under the enablement requirement of section 112," it is well settled that "the PTO bears an initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by that claim is not adequately enabled by the description of the invention provided in the specification of the application; this includes, of course, providing sufficient reasons for doubting any assertions in the specification as to the scope of enablement." In re Wright, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).

"Although the statute does not say so, enablement requires that the specification teach those in the art to make and use the invention without 'undue experimentation.'" In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404

(Fed. Cir. 1988).[23] That some experimentation may be required is not fatal; the issue is whether the amount of experimentation is 'undue.'" In re Vaeck, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991) (emphasis original). In any case, as explained in PPG Indus., Inc. v. Guardian Indus. Corp., 75 F.3d 1558, 1564, 37 USPQ2d 1618, 1623 (Fed. Cir. 1996), undue experimentation has little to do with the quantity of experimentation; it is much more a function of the amount of guidance or direction provided:

> [T]he question of undue experimentation is a matter of degree. The fact that some experimentation is necessary does not preclude enablement; what is required is that the amount of experimentation "must not be unduly extensive." Atlas Powder Co. v. E.I. DuPont de Nemours & Co., 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir. 1984).

We find that the examiner has set forth a reasonable basis for his conclusion that the scope of protection provided by the claims is not adequately enabled by the description of the invention provided in the specification, which appellants have not rebutted by evidence or argument. Accordingly, the rejection of the claims under 35 U.S.C. § 112, first paragraph, for lack of enablement is affirmed.

Appellants argue that "[d]ata has been submitted in the application and subsequently showing the efficacy of two species of inhibitors, antibodies to

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[23] Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman [230 USPQ 546, 547 (Bd.Pat.App.Int. 1986)]. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims (footnote omitted). In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

Mac-1 and peptide inhibitors." Appeal Brief, page 14 (emphasis in original) (citing the examples at pages 22-23 of the specification, as well as an abstract by Simon 1999).[24] According to appellants, the specification provides further support, defining the integrins and ligands, the classes of compounds that may be used, including antibodies, peptides and peptidomimetics, methods for screening for compounds as well as methods of computer aided design. See id. at 15.

The example at pages 22-23 of the specification, i.e., Example 2, is drawn to the use of a single anti-Mac-1 antibody, M1/70, in rabbits. See Specification, page 22. The rabbits were sacrificed after two weeks, and the inventors concluded that there "was a profound inhibition of experimental restenosis by M1/70, equal to or greater that the inhibition achieved in this same animal model by 'gold-standard' experimental antiproliferative agents such as heparin and others." Id. at 23.

Thus, the specification demonstrates that a single antibody, M 1/70, which binds to Mac-1, prevents restenosis in a rabbit experimental model. Appellants' claim 1, however, is drawn to compounds "selected from the group consisting of antibodies and antibody fragments that are immunoreactive with the integrins or integrin-ligands and which block the interaction of the integrins or integrin-ligands with vascular cells; molecules which inhibit expression of the integrins or integrin-ligands, and peptides and peptidomimetics derived from the integrins or integrin-

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[24] Simon et al. (Simon 1999), "Integrin function in Vascular Injury," Circulation, Vol. 100, Supp. 1, Abstract No. 1742 (1999).

ligands which block the interactions of the integrins or integrin-ligands with vascular cells or tissues," wherein the integrins may be Mac-1 (CDIIb/CD18), LFA-1 (CD11a/CD18), p150,95 (CD11cCD18), and CD11D/CD18." Thus, appellants' example of a single therapeutic compound is not commensurate in scope with all of the diverse therapeutic compounds encompassed by the method of claim 1.

Moreover, the specification compares the results to the "gold standard" heparin, which Diamond teaches is an adhesive ligand for Mac-1. Dangas, however, teaches that "heparin has failed to show beneficial effects on restenosis [in humans]." Id. at 431, first column, last paragraph. Thus, Dangas provides evidence of the unpredictability of the art, as the antibody tested in the specification, M1/70, which was reported by the inventors to have "a profound inhibition of experimental restenosis by M1/70, equal to or greater that the inhibition achieved in this same animal model by 'gold-standard' experimental antiproliferative agents such as heparin," but that "gold standard," heparin, was in fact shown by Dangas to have no beneficial effects on restenosis.

As to Simon 1999, appellants have not demonstrated how the data presented in that abstract tracks the teachings in the specification. See, e.g., MPEP 2164.05. Thus, appellants citation of that reference is also not found to be convincing. Finally, we acknowledge the teachings of the specification which define the integrins and ligands, the classes of compounds that may be used, including antibodies, peptides and peptidomimetics, methods for screening for compounds as well as methods of computer aided design. Appellants do not,

however, provide working examples other than Example 2, discussed above, and the examiner has provided sufficient evidence as to the unpredictability of the art and has set forth a reasonable explanation as to why the scope of protection provided by that claim is not adequately enabled by the description of the invention.

Appellants assert further that the examiner has provided no support for his allegations other than Welt, relying only on allegations and argument. See Reply Brief, page 10; see also Appeal Brief, pages 15-16. Appellants contend that Welt is one of the inventors of the instant application, and that the examiner has taken his statements out of context. See id.

First, as acknowledged by appellants in the Reply Brief, the examiner cited and relied on multiple references in setting forth the enablement rejection. See, e.g., Examiner's Answer, pages 15-17. As to Welt, while appellants contend that the examiner has taken a quote out of context, and provides further support for the enablement of the invention, appellants point to nothing in Welt to support those assertions. As discussed above, the examiner's assertion based on Welt that animal models are often not predictive of human pathology is supported by the discussion above, as the specification states that the M1/70 antibody performs as well as the "gold standard" heparin, yet Dingas teaches that heparin has no effect on restenosis in human trials.

Appellants next contend that the references cited by the examiner do not support the enablement rejection. See Reply Brief, page 11. Specifically, with respect to Pimanda, appellants assert that the examiner has again taken a quote

out of context, as the authors state further that therapies in three broad areas, such as gene transfer, gene modification, and gene eluting therapies have emerged. See id. at 12.

Pimanda, published in 2003, after appellants 1997 date, specifically states, as noted by the examiner, that "[f]rom the 1980's to the present, numerous drugs tested in animal models – particularly the pig – have suggested benefit, although until recently none have shown benefit in humans." Id. at 102, column 1. The reference then goes on to state that "[t]herapies in 3 broad areas have recently emerged." Id. (emphasis added). One skilled in the art, reading that statement in a publication dated 2003, would not find the following discussion to be indicative of the state of the art of those therapies in 1997, the filing date claimed by the instant application. Moreover, appellants have not pointed out how the discussion of those three areas of therapies discussed by Pimanda is supported by the instant disclosure as filed.

With respect to Fattori, appellants assert that Fattori is "an excellent review of the prior art compounds that have not worked to prevent restenosis." Reply Brief, page 12. In addition, Appellants note, that while Fattori "provides a long list of other promising compound," they are not claiming the use of any of those compounds. See id.

As noted by the examiner, Fattori, also published in 1993, notes that much research into the use of drugs to prevent restenosis has been done, "but none have proven to be effective." Id. at 248, column 1, under "Preventing Restenosis." The reference goes on to state that:

> Many different biological mechanisms contribute to restenosis and drugs that target only one pathway for a restricted period may have limited value in a multifactorial process. Experience with systemically administered drugs, such as antiplatelet agents, anticoagulants, calcium-channel blockers, angiotensin-converting-enzyme inhibitors, cholesterol-lowering agents, and antioxidants, has proven almost universally negative. These agents were previously tested in animal models and found to be beneficial. The lack of efficacy in human studies may be in part due to insufficient concentration of drug at the injury site or lack of chronic dosing. In general, although animal models provide new insight into the mechanisms of restenosis, biological and mechanical differences meant that therapeutic success of anti-restenotic therapies was not achieved in human beings.

Id. Thus, Fattori in fact supports the examiner's contention that the treatment of restenosis, as late as 2003, was unpredictable.

Appellants assert that "[t]he examiner has focused on all kinds of things that can go wrong, ignoring the data in the application and which was provided subsequently [by the Topol reference]." Reply Brief, pages 10-11. According to appellants, they have provided in vivo evidence "showing that an antibody to at least one of the claimed integrins was effective in an animal model and in combination with independent third parties have provided evidence that another completely different kind of molecule, a peptide, derived from the integrin ligand urokinase receptor, was also effective." Appeal Brief, page 16.

Appellants' arguments are again found not to be persuasive. The examiner has provided reasoning and evidence that the specification does not enable one skilled in the art to practice the full invention of claim 1.

Topol teaches, as noted by the examiner, see Supplemental Examiner's Answer, page 14, that "[a] large number of pharmacological agents have failed to

reduce restenosis or improve long term clinical outcomes, and the only large-scale trial that reported an effect was the 23% reduction in clinical recurrence at 6 months using abcixmab, a monoclonal antibody fragment directed against the β3 integrin." Topol, page 479, far right column, first full paragraph. Thus Topol, as also noted by the examiner, supports the unpredictability of treating restenosis in teaching that a large number of pharmacological agents have failed to reduce restenosis, but also supports the prior art rejection over Genetta, discussed below, by stating that the only large scale drug that showed an effect on the reduction of restenosis, is a trial using the monoclonal antibody abcixmab. Note that Topol also teaches that "[a]bcixmab bolus with infusion given at the time of coronary angioplasty improves outcomes as long as 3 years after the procedure." See Topol, abstract.

Thus, Topol supports the examiner's position that the treatment of restenosis, at the time of filing of the instant application, was unpredictable. Therefore, it is unclear how Topol supports the enablement of the instant specification, as it only discusses the use of the abcixmab antibody, which appellants argue has no effect on restenosis. See Appeal Brief, page 29.

The claimed method is very broad, encompassing a multitude of compounds of different structures and functions, while appellants, as discussed above, have provided only a single working example. Moreover, while the specification describes classes of compounds that may be used, such as antibodies and peptidomimetics, how to screen for compounds that may have efficacy in the claimed therapeutic methods, the examiner has adequately

rebutted the presumption of enablement by providing evidence of the high level of unpredictability associated with the therapeutic treatment of restenosis. Thus, it would require an undue amount of experimentation by the skilled artisan to practice the therapeutic method of claim 1 without further guidance from appellants. As stated by the Court of Appeals for the Federal Circuit, our reviewing court,

> Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. See Brenner v. Manson, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966) (stating, in context of the utility requirement, that "a patent is not a hunting license." It is not a reward for the search, but compensation for its successful conclusion.) Tossing out the mere germ of an idea does not constitute enabling disclosure.

Genentech, Inc. v. Novo Nordisk A/S, 108 F.2d 1361, 1366, 42 USPQ2d 1001, 1005 (Fed. Cir. 1997).

As to claims 6 and 10, appellants argue that the claim is specific to molecules inhibiting Mac-1, and claim 10 is specific to antibodies inhibiting binding to Mac- 1. See Reply Brief, page 13. According to appellants, "[t]hese claims are clearly enabled. They are not drawn to "any compound" as stated by the examiner, but are limited by structure as well as function." Id.

These arguments have not been considered, as appellants did not argue claims 6 and 10 independently in the Appeal Brief, but have first presented arguments as to the separate patentability of those claims in the Reply Brief. See 37 CFR 41.37 (c)(1)(vii) (2006).

ANTICIPATION

Claims 1-6, 8 and 10-12 stand rejected under 35 U.S.C. § 102 (a) or (b) as be anticipated by Genetta[25] as evidenced by Schwarz,[26] Bendeck,[27] Wu[28] and the ERASER Investigators.[29] As appellants do not argue the patentability of the claims separately, we focus our analysis on independent claim 1.

Genetta is cited for teaching that clinical trials have shown "that abciximab can reduce the incidence of abrupt closure and restenosis associated with PTCA [percutaneous transluminal coronary angioplasty] performed in high risk patients, play[ing] a role in the treatment of unstable angina and acute therapy of myocardial infarctions." Examiner's Answer, page 20. The examiner notes that the reference is silent on the Mac-1 binding properties of abcixmab. See id.

Schwarz is cited for its disclosure that the abciximab antibody binds to the I-domain of the Mac-1α subunit and thus binds to Mac-1. See id. In addition, "Schwarz [ ] provide[s] evidence that the GPIIb/IIIa-blocking antibody fragment abciximab could inhibit the binding of fibrinogen, iC3b and the coagulation factor

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[25] Genetta teaches the abciximab antibody, which is essentially the same as the c7E3 and the REoPro antibody. See Examiner's Answer, page 21. Thus the Simon and Coller references are cumulative to Genetta, as they teach the use of the c7E3 antibody, and we will not separately address those rejections.

[26] Schwarz et al. (Schwarz), "The GP IIb/IIIa inhibitor abciximab (c7E3) inhibits the binding of various ligands to the leukocyte integrin Mac-1 (CD11b/Cd18, αMβ2)," Thrombosis Research, Vol. 107, pp. 121-128 (2002).

[27] Bendeck et al. (Bendeck), "The β3 Integrin Antagonist m7E3 Reduces Matrix Metalloproteinase Activity and Smooth Muscle Cell Migration," Journal of Vascular Research, Vol. 38, pp. 590-99 (2001)

[28] Wu et al. (Wu), "Mechanisms Involved in the Inhibition of Neointimal Hyperplasia by Abciximab in a Rat Model of Balloon Angioplasty," Thrombosis Research, Vol. 101, pp. 127-38 (2001).

[29] The ERASER Investigators, "Acute Platelet Inhibition With Abciximab Does Not Reduce In-Stent Restenosis (ERASER Study), Circulation, Vol. 100, pp. 799-806 (1999).

X to Mac-1 and that the adhesion of the THP-1 cells to immobilized ICAM-1 and to fibrinogen was reduced significantly by abcixmab." Id.

Bendeck and Wu are cited for teaching "that the 7E3 antibody can reduce smooth muscle cell migration following vascular injury which resulted in a decrease in intimal size," explaining why treatment of c7E3 (abcixmab, RecPro) have been associated with a reduction in coronary events and the need for revascularization. Id. at 21.

The ERASER Investigators note, as set forth by the examiner, "that potent platelet inhibition does not reduce in-stent restenosis in their study," but "notes that these results should not necessarily be extrapolated to balloon angioplasty because the mechanisms of restenosis differ." Id.

We recognize that in order for a prior art reference to serve as an anticipatory reference, it must disclose every limitation of the claimed invention, either explicitly or inherently. See In re Schreiber, 128 F.3d 1473, 1477, 44 USPQ2d 1429, 1432 (Fed. Cir. 1997). We find that Genetta anticipates the invention of claim 1, and the rejection is affirmed.

Appellants argue that Genetta "does not disclose binding of Mac-1 by abciximab," and "does not disclose inhibiting leukocyte adhesion." Appeal Brief, pages 27-28.

While we agree that Genetta does not disclose that abcixmab is immunoreactive with Mac-1, the examiner relies on Schwarz to demonstrate that is an inherent property of the antibody. Genetta teaches on page 251, column 1, that "[a]bciximab is a humanized chimeric fragment of 7E3. 7E3 is a murine

antibody directed against the integrin glycoprotein IIb/IIIa receptor located on platelets." Genetta importantly teaches further that "[c]linical trials have indicated that abciximab can reduce the incidence of abrupt closure and restenosis associated with percutaneous transluminal coronary angioplasty (PTCA) performed in high-risk patients," and that "[a]bcixmab is currently approved for the prevention of abrupt closure associated with PTCA in patients at high risk for this event." Id. (emphasis added). Thus, Genetta teaches the use of the antibody abcixmab in inhibiting or reducing restenosis in a blood vessel following injury to vascular tissue in a region of the blood vessel of a patient in need of treatment thereof.

Schwarz is cited for teaching that abcixmab binds, and is thus immunoreactive with, Mac-1. Specifically Schwarz discloses in the abstract that they describe "binding of abcixmab to Mac-1 on stimulated monocytes. Thereby, abciximab inhibits binding of the ligands fibrinogen, ICAM-1, iC3b and factor X," concluding that "the inhibition of Mac-1 could provide additional clinical benefits of abciximab beyond the well described blockade of GP IIb/IIIa." Moreover, the reference teaches that "abciximab binds specifically to Mac-1 on monocytes," and "is specific for the α-subunit of Mac-1." Id. at 125, column 1. In addition, as taught by Schwarz, "[t]he same results were obtained with Mac-1 expressing THP-1 cells.

Thus, Genetta teaches that the abciximab antibody can reduce the incidence of abrupt closure and restenosis associated with percutaneous transluminal coronary angioplasty (PTCA) performed in high-risk patients, and

Schwarz teaches that abciximab is immunoreactive with Mac-1. Therefore, Genetta meets all of the limitations of claim 1.

In response to the examiner's contention that Schwarz demonstrates that abciximab binds to Mac-1, appellants cite Mickelson[30] for the proposition that abciximab does not bind directly to Mac-1. See Appeal Brief, page 28. Moreover, according to appellants, the ERASER study supports their position by teaching that abciximab does not reduce in-stent restenosis. See id. Appellants point to Example 2 of the specification, which demonstrates that their anti-Mac-1 antibody reduces both in-stent and balloon angioplasty injured restenosis. See id.

Appellants' arguments are not found to be convincing. As noted by the examiner, Mickelson, although noting that 7E3 does not bind to leukocytes directly, in fact discloses "that both the 7E3 and chimeric 7E3 antibodies blocked two Mac-1 (CD11b)-dependent adhesive properties, namely adhesion to fibrinogen and adhesion to ICAM-1." Examiner's Answer, page 54. Mickelson also teaches that 7E3 antibody reduces clinical restenosis in coronary angioplasty, see page 103, first column, stating in the abstract that 7E3 "influences CD11b expression in whole blood," and that "[m]odulation of platelet and leukocyte activation and interaction by chimeric 7E3 fab may contribute to an improved outcome after coronary angioplasty." Moreover, as further noted by the examiner, Schwarz, which was published after the Mikelson publication,

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[30] Mickelson et al. (Mickelson), "Chimeric 7E3 Fab (ReoPro) Decreases Detectable CD11b on Neutrophils from Patients Undergoing Coronary Angioplasty," JACC, Vol. 33, pp. 97-106 (1999).

describes binding of abciximab to Mac-1, and in particular, the I-domain of the Mac-1α subunit. See Examiner's Answer, page 54. All that is required by the claim is that the antibody be immunoreactive[31] with the integrin, and Schwarz clearly demonstrates that 7E3 (i.e., abcixmab) is immunoreactive with the integrin Mac-1.

As to the ERASER Investigators, the examiner points to the statement in the reference that the results from in-stent restenosis should not necessarily be extrapolated to balloon angioplasty because the mechanisms of restenosis differ, and "[a]ppellant[s] ha[ve] not provided objective evidence to indicate that the 7E3 antibody failed to inhibit restenosis in those patients undergoing balloon angioplasty." Examiner's Answer, page 55.

Appellants further cite Deitch[32] and Simon 2000[33] to demonstrate that abcixmab has no effect on restenosis, concluding that "[t]he claimed method is not anticipated because Genetta does not disclose an antibody that specifically binds Mac-1 nor a compound that specifically inhibits or reduces leukocyte integrin-mediated adhesion or function." Appeal Brief, page 29 (emphasis in original).

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[31] Note that Stedman's Medical Dictionary, 24th Edition, (1982), copy of definition attached, defines "immunoreaction" as an "[a]n immunologic reaction, especially *in vitro* between antigen and antibody." Thus, "immunoreactive" does not necessarily require binding *in vivo*, and supports the panel's claim construction that there is no requirement that the compound reduces leukocyte integrin-mediated adhesion or function through its immunoreactivity with the integrin or integrin ligand.

[32] Deitch et al. (Deitch), "Effects of β3-Integrin Blockade (c7E3) on the Response to Angioplasty and Intra-Arterial Stenting in Atherosclerotic Nonhuman Primates," Arterioscler. Thromb. Vasc. Biol., Vol. 18, pp. 1730-1737 (1998).

[33] Simon et al. (Simon 2000), "Decreased neointimal formation in *mac-1-/-* mice reveals a role for inflammation in vascular repair after angioplasty," J. Clin. Invest., Vol. 105, pp. 293-300 (2000).

Appellants' arguments are not commensurate in scope with the claimed subject matter, as all that is required by the claim is that the abcixmab antibody be immunoreactive with the Mac-1 integrin, which, as discussed above, is demonstrated by Schwarz. With respect to Deitch, as noted by the examiner, Dietch relates to a study of "the effects on the response to experimental angioplasty and stenting of arteries in cynomologous monkeys with established atherosclerosis," which "is not the same circumstances as treating patients in need undergoing cardiovascular surgeries and procedures as taught by the prior art or encompassed by the claimed invention." Examiner's Answer, page 56 (emphasis in original). The examiner also concludes that Simon does not rebut the prima facie case of anticipation, see id. at 57, as it also relates to an animal model, whereas Genetta teaches that "[c]linical trials have indicated that abciximab can reduce the incidence of abrupt closure and restenosis associated with percutaneous transluminal coronary angioplasty (PTCA) performed in high-risk patients."

In the Reply Brief, appellants assert that

> treatment of an acute condition-myocardial infarction-is just that: a treatment over a short defined time . . . . In contrast, appellants require administration over a period of time "typically until healing has occurred, which may be as long as six months following vascular intervention, although more typically will be four to six week s or until acute inflammation has subsided" . . . . The administration of the antibody, even if it met every other claim limitation (which it does not) would not be effective in preventing restenosis because it is not administered in an effective amount-which is not only dosage but length of time of administration. To prevent restenosis, one must administer the treatment over a prolonged period of time-weeks to months.

> The antibody does not have the claimed specific activity-it is active in preventing platelet aggregation, not in inhibiting or reducing leukocyte integrin mediated function. As importantly, the prior art does not describe prolonged administration, which is essential for preventing or treating stenosis or restenosis.

Id. at 14-15.

Appellants assert further that Schwarz does not make up for the deficiencies in Genetta, as Schwarz demonstrates that the binding of abcixmab to Mac-1 is not selective. Reply Brief, page 16. Appellants argue, citing Bendeck,[34] that the antibody of Genetta was not used to prevent restenosis but in studies relating to ischemia. See Reply Brief, page 17. Appellants conclude that "the prior art relating to the use of c7E3 does not anticipate the claimed subject matter. The antibody is not specific; the antibody was used to treat acute ischemia; and the antibody was administered for only very short periods of time. In contrast, the claims require a specific inhibitor; treatment or prevention of a chronic condition, restenosis or stenosis due to excessive tissue proliferation; and an effective amount of compound which requires long term administration." Id. at 17-18.

Again, appellants' arguments are not found to be convincing. As noted above in the section drawn to claim construction, claim 1 reads on any measurable reduction of restenosis, and Genetta clearly teaches that the antibody abciximab can reduce the incidence of restenosis associated with PTCA. Appellants assertion that they "require administration over a period of time 'typically until healing has occurred, which may be as long as six months

following vascular intervention, although more typically will be four to six weeks or until acute inflammation has subsided'" is not commensurate in scope with the claimed subject matter, and appellants are reading limitations from the specification into the claims, a practice that the Court of Appeals for the Federal Circuit, our reviewing court, cautions against. See SuperGuideCorp. v. DirecTV Enterprises, Inc., 358 F.3d 870, 875, 69 USPQ2d 1865, 1868-69 (Fed. Cir. 2004) ("Though understanding the claim language may be aided by explanations contained in the written description, it is important not to import into the claim limitations that are not part of the claim. For example, a particular embodiment in the written description may not be read into a claim when the claim language is broader than the embodiment.").

Thus, appellants appear to be relying on a preferred embodiment, as the specification teaches:

> In general, this will result in a patient being systemically with the inhibitor of integrin mediated leukocyte adherence or function for between zero and 24 to 48 hours prior to surgery or vascular intervention, preferably about two hours, and for a period of time following surgery, typically until healing has occurred, which may be as long as six months following vascular intervention, although more typically will be for four to six weeks or until acute inflammation has subsided.

Id. at 21-22. The method of claim 1, however, requires no specific treatment schedule: All that is required is treatment that results in a measurable inhibition or reduction of stenosis or a measurable reduction in restenosis.

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[34] Bendeck et al. (Bendeck), "The β3 Integrin Antagonist m7E3 Reduces Matrix Metalloproteinase Activity and Smooth Muscle Migration," J. Vasc. Res., Vol. 38, pp. 590-99 (2001).

Moreover, Genetta teaches at page 253, second column, that patients receiving the abcixmab antibody received a bolus dose given 10 minutes prior to PTCA followed by a 12 hour constant infusion had a 35% reduction in deaths and cardiac reduction, a measurable reduction in the incidence of restenosis, and therefore some level of healing must have occurred.

As to Schwarz, as noted in above, Schwarz teaches that abciximab binds specifically to Mac-1 on monocytes, and is specific for the α-subunit of Mac-1. Moreover, Mikelson, cited by appellants, teaches both the 7E3 (i.e., abciximab) and chimeric 7E3 antibodies blocked two Mac-1 (CD11b)-dependent adhesive properties, namely adhesion to fibrinogen and adhesion to ICAM-1, thus teaching that 7E3 specifically inhibits or reduces leukocyte integrin-mediated adhesion or function. The fact that the art does not definitively demonstrate that the administration of abcixmab results in a reduction of restenosis through its immunoreactivity with Mac-1 is irrelevant, as there is no requirement in the claim that the antibody reduce restenosis through it ability to bind an integrin such as Mac-1, but only that it have the properties of reducing integrin-mediated adhesion or function and is immunoreactive with a ligand such as Mac-1.

For the reasons set forth above, we affirm the rejection of claims 1-6, 8, and 10-12 as being anticipated by Genetta.

Claims 1-6, 8, and 10-12 stand rejected under 35 U.S.C. § 102(e) as being anticipated by Co.

As set forth in the rejection, Co teaches

> methods of therapeutic and prophylactic treatment of ischemia-reperfusion injury in various modalities including cardiac surgery such as coronary artery bypass and elective angioplasty (columns 17-18, overlapping paragraph and column 18, paragraph 3-4) wherein the L-selectin-specific antibodies can [be] used in combination with other humanized or human antibodies reactive with CD11b (i.e. Mac-1) (column 18, paragraph 1). Co [ ] teach[es] that the antibodies can be administered before[, sic] during or after the administration of thrombolytic agents or angioplasty, including doses of 0.01-10 mg/kg, 0.14-5 mg/kg and 0.3-3 mg/kg (column 18, paragraph 4). Co [ ] teach[es] administering the antibodies parenterally in pharmaceutical compositions along with suitable carriers encompassed by the claimed invention in effective amounts that would [be] known or apparent to the skilled artisan (column 20, paragraph 1-4).

Examiner's Answer, page 25.

According to the examiner, "[t]he claimed functional limitations would be inherent properties of the referenced methods encompassed by the referenced combination therapy including the use of anti-CD11b antibodies in methods of therapeutic and prophylactic treatment of ischemia-reperfusion injury in various modalities including cardiac surgery such as coronary bypass and elective angioplasty resulting in the inhibition or reduction of stenosis and/or restenosis." Id. at 26. The examiner asserts further that "[a]lthough the reference does not disclose the limitations of stenosis and restenosis per se, these claimed endpoints would be achieve[d] by the administration of effective amounts . . . of CD11b/Mac-1-specific antibodies in the same patient populations . . . targeted and encompassed by the claimed methods." Id.

Appellants argue that the examiner admitted on page 27 of the office action of October 30, 2003, that Co does not disclose the limitations of stenosis and restenosis, thus, "[a]s Co does not disclose the same method defined in the

present claims, the claimed method is not anticipated." Appeal Brief, page 32. Appellants assert further that the use of the L-selectin antibody in Co "is for the treatment of ischemia-reperfusion injury," which "is where tissue dies from lack of oxygen due to acute blockage; not where occlusion of a blood vessel develops over a period of weeks or months due to overproliferation of cells. These are just the opposite – one is characterized by acute blockage and cell death and the other by the development of a chronic blockage over time due to too much cell proliferation." Reply Brief, page 20.

It is the examiner's burden to demonstrate that the prior art reference discloses every limitation of the claimed invention, either explicitly or inherently, and thus serves as an anticipatory reference. As we find that the examiner has not met that burden, this rejection is reversed.

Co teaches the use of anti-L-selectin antibodies may be used in the treatment of inflammatory diseases. See Co, abstract. In addition, Co teaches that the L-selectin antibodies of that invention with other antibodies reactive with other adhesion molecules, wherein the adhesion molecules may be CD11a, CD11b, CD18, E-selectin, P-selectin and ICAM-1. See id. at Col. 18, lines 13-19. Co also teaches that "ischemia-reperfusion injury is reduced or prevented by combination of a thrombolitic agent or of PTCA with humanized or human anti-L-selectin antibodies," wherein the antibodies are administered at the same time as the administration of the thrombolytic agents or PTCA. Id. at lines 43-50.

The examiner asserts that the above teaches the method of claim 1, contending that the claimed functional limitations would be inherent properties of

the referenced methods. According to the examiner, including the use of anti-CD11b antibodies in methods of therapeutic and prophylactic treatment of ischemia-reperfusion injury would result in the inhibition or reduction of stenosis and/or restenosis in the same patient populations targeted and encompassed by the claimed methods. No evidence, however, has been provided by the examiner to support that assertion. Therefore, the examiner has not met the burden of demonstrating that Co anticipates the claimed method, and we are compelled to reverse the rejection.

Claims 1-6, 8, and 10-12 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Todd. As appellants do not argue the patentability of the claims separately, we focus our analysis on independent claim 1.

As set forth by the examiner,

> Todd teach[es] methods of reducing tissue damage occurring at an inflammatory site in a host experiencing a phagocyte-mediated inflammatory conditions, including inflammation from myocardial infarction or ischemia-reperfusion injury and the insertion of balloon catheters in the circulatory system with CD11b-/Mac-1-specific antibodies (see entire document, including Claims). Todd [ ] teach[es] providing the CD11b-specific antibodies prior to intervention as well as in single or multiple doses to attenuate the inflammatory responses (see column 1, paragraph 2). Todd [ ] exemplif[ies] 1 mg/kg dosing (see column 6, paragraph 1 and column 9, paragraph 1).

Examiner's Answer, page 26.

Moreover, according to the examiner,

> Todd [ ] teach[es] that myocardial ischemia results from occlusion, reperfusion in the presence of critical stenosis or narrowing of a blood vessel (e.g. column 6, paragraph 4). One of ordinary skill in the art would have immediately envisaged that providing the anti-CD11b antibody in therapeutic methods would

> have encompassed providing the antibody in a pharmaceutical composition comprising at least a "solution" at the time the invention was made. One of ordinary skill in the art at the time the invention was made would have immediately envisaged that the referenced teaching the insertion of balloon catheters in the circulatory system would have referred to angioplasty at the time the invention was made.

Id.

In addition, the examiner contends that "[a]lthough the reference does not disclose the limitation of restenosis per se, these claimed endpoints would be achieve[d] by the administration of effective amounts (e.g. to attenuate inflammatory responses . . . and reduce tissue damage, to inhibit undesired neutrophil functions . . .) of CD11b/Mac-1-specific antibodies in the same patient populations . . . targeted and encompassed by the claimed methods." Id. at 27. Thus, the examiner concludes, "[t]he claimed functional limitations would be inherent properties of the referenced methods encompassed by the referenced combination therapy including the use of anti-CD11b antibodies in methods of therapeutic treatment of ischemia-reperfusion injuries resulting in the inhibition or reduction of stenosis and/or restenosis." Id.

Again, we note that it is the examiner's burden to demonstrate that that the prior art reference discloses every limitation of the claimed invention, either explicitly or inherently, and thus serves as an anticipatory reference. We find that the examiner has met that burden, and the rejection is affirmed.

Todd teaches a method of reducing tissue damage occurring at an inflammatory site through the administration of a monoclonal antibody that binds to the CD11b part of the CD11/CD18 glycoprotein (i.e., Mac-1), wherein the

antibody "will inhibit the CD11/CD18 adhesion dependent cellular interactions of such cells reflecting their [immunological] inflammatory response which contributes to such damage." Todd, claim 1. Todd teaches that the use of the anti-Mac-1 antibody, MY904, "in the setting of reperfusion myocardial injury is shown to be effective in decreasing the size of anticipated infarction by a significant percentage when administered in vivo prior to reperfusion of ischemic myocardium." Id. at column 4, lines 41-46. One manner in which the antibody may be used taught by Todd is during the surgical treatment of balloon catheterization, wherein a balloon catheter is inserted into the circulatory system and directed to the blood clot area for eliminating the blockage. See id. at column 10, lines 21-28. A single dose or multiple doses may be administered. See id. at column 10, lines 28-30.

Todd thus teaches a method that reads on the method of claim 1. Claim 1 is drawn to a method of administering a compound which "specifically inhibits" or "reduces" leukocyte integrin-mediated adhesion or function, wherein the elected integrin is Mac-1, wherein the compound is selected from the group consisting of "leukocyte integrin-mediated adhesion or function," and wherein stenosis or restenosis is inhibited or reduced. As defined by Todd, the anti-Mac-1 antibody, MY904, inhibits the CD11/CD18 adhesion dependent cellular interactions. In addition, as the antibody is administered during the surgical procedure of balloon catheterization, the patient population is the same, as claim 1 is drawn to a method of inhibiting . . . restenosis of a blood vessel following injury to vascular tissue. As the therapeutic agent is the same, i.e., an anti-Mac-

1 antibody that inhibits CD11/CD18 adhesion dependent cellular interactions, and the patient population is the same, the result of reducing restenosis would be an inherent result of the method. Note that "[i]t is a general rule that merely discovering and claiming a new benefit of an old process cannot render the process again patentable." In re Woodruff, 919 F.2d 1575, 1578, 16 USPQ2d 1934, 1936 (Fed. Cir. 1990). See also Bristol Myers Squibb v. Ben-Venue Laboratories, 246 F.3d 1368 (Fed. Cir. 2001) ("Newly discovered results of known processes directed to the same purpose are not patentable because such results are inherent.").

Appellants assert that "the Examiner has admitted on page 28 of the Office Action that Todd does not disclose the limitation of treating restenosis," and that "[s]ince Todd does not disclose each and every limitation, Todd does not anticipate the claimed invention." Appeal Brief, page 32. According to appellants, "the patient class is different, the mechanism is different, and the disorder to be treated is different from the claimed method." Reply Brief, page 21.

Appellants' arguments have been considered, but are not found to be convincing. We agree that Todd fails to teach treatment of restenosis, per se. As discussed above, however, Todd teaches administering a therapeutic antibody that meets all of the limitations of the therapeutic antibody of claim 1, to the same patient population, therefore, the result of reducing restenosis would be an inherent property of the method. While appellants assert that the patient class is different, the mechanism is different, and the disorder to be treated is

different from the claimed method, they have provided no evidence to that effect, and arguments of counsel cannot take the place of evidence in the record. See In re Scarbrough, 500 F.2d 560, 566, 182 USPQ 298, 302 (CCPA 1974); In re DeBlauwe, 736 F.2d 699, 705, 222 USPQ 191, 196 (Fed. Cir. 1984).

OBVIOUSNESS

Claims 1-6, 8 and 10-12 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over the combination of Co and/or Todd, Simon 1995, Mazzzone, Ikeda, Inoue and Rogers.

As appellants did not argue the claims separately, the claims stand or fall together. As claim 1 has found to be anticipated by Todd, and as anticipation is the epitome obviousness, see In re Francalossi, 681 F.2d 792, 794, 215 USPQ 569, 571, (CCPA 1982); Structural Rubber Products Co. v. Park Rubber Co., 749 F.2d 707, 717, 223 USPQ 1264, 1271 (Fed. Cir. 1984), we also affirm this rejection to the extent it is based on Todd.

CONCLUSION

Because we find that the examiner has met his burden of setting forth a prima facie case of unpatentability, we affirm the rejections under 35 U.S.C. § 112, first paragraph, on the basis of lack of adequate written description and lack of enablement. We also affirm the prior art rejections as they are based on Genetta and Todd. We reverse, however, the prior art rejections over Co on the basis that the examiner has failed to meet his burden that Co anticipates the claimed methods.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 CFR § 1.136(a).

AFFIRMED

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